Inspections, Compliance and Imports

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Acronyms

- BLA- Biologics License Application
- CBER – Center for Biologics Evaluation and Research
- FFDCA – Federal Food, Drug and Cosmetic Act
- IND – Investigational New Drug application
- OCBQ – Office of Compliance and Biologics Quality

- OCTGT – Office of Cellular, Tissue and Gene Therapies
- ORA – Office of Regulatory Affairs (FDA field
- PHSA – Public Health Service Act

Surveillance

Summary

- FDA's mission is to protect the public health
- Inspections, issuance of compliance or regulatory actions, and review of imports are, for the most part, surveillance activities that help to ensure the public health.
- We also conduct inspections prior to approval of an application, while under IND or during review of a marketing application. Actions may also result from these activities

Products regulated solely under section 361 of the PHSA

Applicability: § 1271.390

- "..applicable only to HCT/Ps described in 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part and to the establishments that manufacture those HCT/Ps"
- If drugs or devices under the FFDCA, or section 351 products, not subject to these regulations. Held to FFDCA and PHSA 351.
- Surveillance inspections

Inspections
§ 1271.400

(a)…you must permit the Food and Drug Administration (FDA) to inspect any manufacturing location at any reasonable time and in a reasonable manner to determine compliance with applicable provisions of this part. The inspection will be conducted as necessary in the judgment of the FDA and may include your establishment, facilities, equipment, finished and unfinished materials, containers, processes, HCT/Ps, procedures, labeling, records, files, papers, and controls required to be maintained under the part. The inspection may be made with or without prior notification and will ordinarily be made during regular business hours.

§ 1271.400

- (b) The frequency of inspection will be at the agency's discretion.
- (c) FDA will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel of the establishment as necessary to determine compliance with the provisions of this part.

§ 1271.440

- (d) FDA's representatives may take samples, may review and copy any records required to be kept under this part, and may use other appropriate means to record evidence of observations during inspections conducted under this subpart.
- In response to comments about (c) we clarified that financial records, personnel records (outside or job training) and internal quality audit records will not be reviewed by FDA during inspections.

§ 1271.440

- (e) The public disclosure of records containing the name or other positive identification of donors or recipients of HCT/Ps will be handled in accordance with FDA's procedures on disclosure of information as set forth in parts 20 and 21 of this chapter.

361 Inspection

- Performed by ORA investigators with specialized training using an established Compliance Program
- New program being developed to cover all 361 HCT/Ps
- Existing 1270 program for “traditional” HCT/Ps recovered before May 25, 2005

Products that meet the definition of drugs and biologics

GMP Inspections: Surveillance

- Section 704 of the FFDCA- authority
- Also Section 351(d) of PHSA for biological products
- Section 510(h) of the FFDCA– biennial for registered firms
- CBER products
  - 21 CFR 600.21 – each licensed establishment biennial
- Not pre-announced

GMP Inspections

- CBER Biological Drugs Post-approval
- "Team Biologics Core Team" member(s) – lead investigator and other GMP investigators
  - Product division from OCTGT– product specialist
  - May be more than one depending on products produced
  - May participate "off-site"

Pre-license Inspections (PLIs)

- Subject to BLA
- May be non-U.S. licensed firm
- May be U.S. licensed firm with a new product under BLA
- May involve several sites
- Necessary for licensure under 21 CFR 601.20(d)

PLIs

- 21 CFR 601.20
  - (a) Determination of compliance with application and applicable standards including GMP
  - (b) Product to be introduced into interstate commerce available for inspection during all phases of manufacture

PLIs

- Focus on subject product, however, all “systems” also covered.
- Process validation data verified – observe manufacture of last conformance lot
- Always pre-announced
- Discussions with manufacturer take place during the review process and inspection is planned to coincide with activity.

Pre-approval (PAI)

- Subject to Prior Approval Supplement under 21 CFR 601.12(b)
  - May be new manufacturing facility
  - May be contract manufacturing facility; generally only drugs and biologics (except testing)
  - May be significant process changes
  - Always pre-announced
  - Discussion with manufacturer during review process and inspection timed to coincide with activity.

CBER PLI/PAI

- Division of Manufacturing and Product Quality, OCBQ/CBER – lead inspector
- CBER product division from OCTGT – product specialist
  - May not participate in PAI, depending on scope of supplement
- ORA District Office investigator

BIMO

- Bioreseach Monitoring (BIMO)
  - Product under IND
    - GLP – Good Laboratory Practice – Part 58
    - GCP– Good Clinical Practice –

      Parts 50 and 312

      Part 56 for Institutional Review Boards (IRBs)
    - GMP – Parts 210-211
  - May inspect sponsor, IRB, clinical investigator(s), non-clinical laboratories, contract research organizations.

BIMO

- BIMO inspections are assigned to the districts from CBER. May be random or tied to a pending BLA.
- Specialized investigators, trained in applicable regulations perform inspection and submit findings to CBER/Office of Compliance and Biologics Quality/ Division of Inspections and Surveillance.

For Cause

- For all products
- May be a result of complaints, recalls, or other information that suggests the need for an inspection

All Inspections

- Investigator(s)/Inspectors(s) display credentials and issue a Notice of Inspection: Form FDA 482
- Exception – the FDA-482 is not issued to foreign establishments.

All Inspections

- At the conclusion of the inspection, a Form FD-483 List of Inspectional Observations may be issued.
- Response not regulatory requirement, but in best interest
  - CBER PLI CBER/PAI – necessary for licensure/approval

FD-483

- “This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above….”

Communication

- Communication is key before (for PLI/PAI), during and after the inspection.
  - For PLI/PAI communication during the review process and inspectional planning
  - For all inspections - ask questions and seek clarification from investigators/inspectors on a regular basis
  - A thorough and thoughtful response is very important – not limited to observations

FDA Actions subsequent to an Inspection

- "Regulatory Procedures Manual"
  - http://www.fda.gov/ora/compliance_ref/rpm/default.htm
  - Regulatory meetings
  - Advisory Actions
  - Enforcement Actions
    - Administrative Actions
    - Legal Actions

Regulatory Meetings

- Unlike most meetings, which are requested by industry, FDA asks industry to come in to meet.
- FDA will often provide an agenda to you prior to the meeting
- Should be taken quite seriously

Warning Letters

- Informal advisory - no legal responsibility to issue warning
- States agency's position, but does not require the agency to take enforcement action
- Require a company response
- Other government agencies notified
- Posted on the website
- Inadequacies in your response will be addressed
- Usually FDA's last attempt to get company's attention before enforcement action

Untitled Letters

- Communication to the industry of concerns
- May ask for a response
- Other federal agencies not advised
- No warning statement

Administrative Actions

- For HCT/Ps approved under BLA
  - License suspension – if imminent danger to health
  - License revocation – or notice to revoke when violations, often repeated, occur
- For HCT/Ps regulated solely under 361
  - Orders for retention, recall, destruction and cessation of manufacturing

Legal Actions

- Seizure
- Injunction
- Consent Decree
- Prosecution

IMPORTS

Products regulated solely under section 361 of the PHSA

HCT/Ps Offered for Import § 1271. 420

- (a) Except as provided in paragraphs (c) and (d) of this section, when an HCT/P is offered for import, the importer of record must notify, either before or at the time of importation, the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the HCT/P is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part, and must provide sufficient information for FDA to make an admissibility decision.

§ 1271.420

- (b) Except as provided in paragraphs (c) and (d) of this section, an HCT/P offered for import must be held intact by the importer or consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA. The HCT/P may be transported under quarantine to the consignee, while the FDA district reviews the documentation accompanying the HCT/P. When FDA makes a decision regarding the admissibility of the HCT/P, FDA will notify the importer of record.

§1271.420

- Revisions made to (a) and (b) from 1270 were to provide clarity and for consistency with agency import policy
- (c) and (d) added due to concerns raised over reproductive HCT/Ps imported under authority of the owner and over potential adverse effects on hematopoietic stem/progenitor cells

§ 1271.420

- (c) This section does not apply to reproductive HCT/Ps regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and donated by a sexually intimate partner of the recipient for reproductive use.

§ 1271.420

- (d) This section does not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the Public Health Service Act and the regulations in this part, except that paragraphs (a) and (b) of this section apply when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission which indicates the need to review the information referenced in paragraph (a) of this section.

Imports for products regulated as Drugs/Biologics

Imports for products regulated as Drugs/Biologics

- Section 801 of the FFDCA would apply.
- Agency intends to use same procedures to facilitate entry for peripheral blood stem/progenitor cells that are not regulated solely under 361;
- If under IND or BLA, submission number should be on incoming documentation

Questions?

–www.fda.gov/cber